The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

PRIORITY DOCUMENT

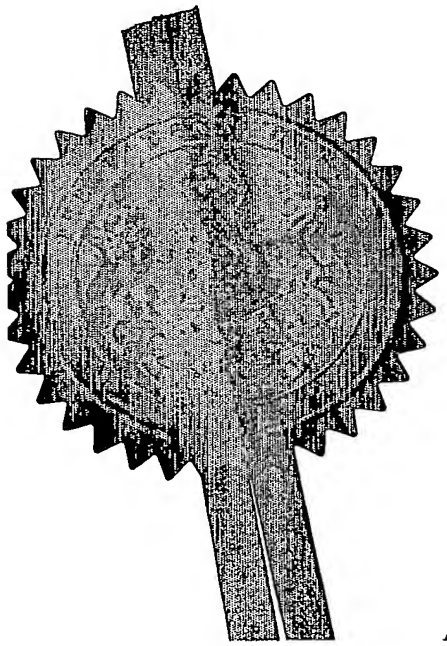
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed P. Mahoney

Dated 11 September 2003

E743705-1 D02934
P01 0 0.00-0219819.0

1/77

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
J
24 AUG 2002
NEWPORT

The Patent Office
THE PATENT OFFICE
27 AUG 2002
NEWPORT

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference

100817

2. Patent application number
(The Patent Office will fill in this part)

0219819.0

24 AUG 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
S-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)*

7822448003

If the applicant is a corporate body, give the country/state of its incorporation

Sweden

4. Title of the invention

NOVEL COMPOUND

5. Name of your agent *(if you have one)*

Kevin Bill

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG

Patents ADP number *(if you know it)*

7822471002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	25
Claim(s)	04
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Date

Authorised Signatory 23/08/2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Jennifer C Bennett - 01625 230148

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) For details of the fee and ways to pay please contact the Patent Office.

NOVEL COMPOUND

The present invention relates to certain heterocyclic compounds, processes and intermediates used in their preparation, pharmaceutical compositions containing them and their use in therapy.

Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved cysteine motif. At the present time, the chemokine superfamily comprises three groups exhibiting characteristic structural motifs, the C-X-C, C-C and C-X_3-C families. The C-X-C and C-C families have sequence similarity and are distinguished from one another on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues. The C-X_3-C family is distinguished from the other two families on the basis of having a triple amino acid insertion between the NH-proximal pair of cysteine residues.

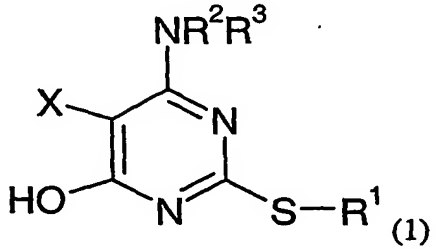
The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils. Examples include human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

The C-X_3-C chemokine (also known as fractalkine) is a potent chemoattractant and activator of microglia in the central nervous system (CNS) as well as of monocytes, T cells, NK cells and mast cells.

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX_3CR1 for the C-X_3-C family. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

The present invention provides compounds of formula (1), pharmaceutically acceptable salts or solvates thereof and *in vivo* hydrolysable esters thereof:



(1)

wherein R^1 is a group selected from C_{3-7}carbocyclyl, C_{1-8}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl; wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from fluoro, nitrile, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, phenyl or heteroaryl; wherein phenyl and heteroaryl are optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_{1-6}alkyl and trifluoromethyl;

wherein R^2 is C_{3-7}carbocyclyl, optionally substituted by 1, 2 or 3 substituents independently selected from:

(a) fluoro, $-OR^4$, $-NR^5R^6$ $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$;

(b) a 3-8 membered ring optionally containing 1, 2 or 3 atoms selected from O, S, $-NR^8$ and whereby the ring is optionally substituted by C_{1-3}alkyl or fluoro; or

(c) phenyl or heteroaryl, each of which is optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-NR^8COR^9$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_{1-6}alkyl and trifluoromethyl;

or R^2 is a group selected from C_{1-8}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl wherein the group is substituted by 1, 2 or 3 substituents independently selected from hydroxy, amino, C_{1-6}alkoxy, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, *N*-(C_{1-6}alkyl)-*N*–(phenyl)amino, *N*-C_{1-6}alkylcarbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N*–(phenyl)carbamoyl, carboxy, phenoxycarbonyl, $-NR^8COR^9$, $-SO_2R^{10}$, $-SO_2NR^5R^6$ and $-NR^8SO_2R^9$;

wherein R^3 is hydrogen or R^2;

R^4 is hydrogen or a group selected from C_{1-6}alkyl and phenyl, wherein the group is optionally substituted by 1 or 2 substituents independently selected from halo, phenyl, $-OR^{11}$ and $-NR^{12}R^{13}$;

R^5 and R^6 are independently hydrogen or a group selected from C_{1-6}alkyl and phenyl wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, phenyl, $-OR^{14}$,$-NR^{15}R^{16}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-SONR^{15}R^{16}$ and $NR^{15}SO_2R^{16}$

or

R^5 and R^6 together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring system optionally containing a further heteroatom selected from oxygen and nitrogen atoms, where the ring system may be optionally substituted by 1, 2 or 3 substituents independently selected from phenyl, $-OR^{14}$, $-COOR^{14}$, $-NR^{15}R^{16}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-SONR^{15}R^{16}$, $NR^{15}SO_2R^{16}$ or C_{1-6}alkyl (optionally substituted by 1 or 2 substituents independently selected from halo, $-NR^{15}R^{16}$ and $-OR^{17}$ groups);

R^{10} is hydrogen or a group selected from C_{1-6}alkyl or phenyl, wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, phenyl, $-OR^{17}$ and $-NR^{15}R^{16}$; and

each of R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14} R^{15}, R^{16}, R^{17} is independently hydrogen, C_{1-6}alkyl or phenyl;

X is hydrogen, halo, cyano, nitro, hydroxy, C_{1-6}alkoxy (optionally substituted by 1 or 2 substituents selected from halo, $-OR^{11}$ and $-NR^{12}R^{13}$), $-NR^5R^6$, $-COOR^7$, $-NR^8COR^9$, thio, thiocyano, C_{1-6}alkylthio (optionally substituted by 1 or 2 substituents selected from halo, $-OR^{17}$, $-NR^{15}R^{16}$), $-SO_2R^{10}$, $-SO_2NR^5R^6$ or a group selected from C_{3-7}carbocyclyl, C_{1-8}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl, wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$ and $-NR^8SO_2R^9$; or an aryl or heteroaryl group, both of which may be optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_1-C_6alkyl or trifluoromethyl groups;

Certain compounds of formula (1) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (1) and mixtures thereof including racemates.

The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Within the present invention it is to be understood that a compound of formula (1) or a salt, solvate or *in vivo* hydrolysable ester thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form and mixtures thereof and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It is also to be understood that certain compounds of formula (1) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms.

The present invention relates to the compounds of formula (1) as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (1) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula (1) as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. Suitable salts include hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, acetates, benzoates, citrates, maleates, fumarates, succinates, lactates, tartrates, oxalates, methanesulphonates or *p*-toluenesulphonates. Pharmaceutically acceptable salts of the invention may also include basic addition salts of the

compounds of formula (1) as hereinbefore defined which are sufficiently acidic to form such salts. Such salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a lithium, sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or an organic amine salt, for example a salt with methylamine, dimethylamine, trimethylamine, triethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine. Other basic addition salts include aluminium, zinc, benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine.

The present invention further relates to an *in vivo* hydrolysable ester of a compound of formula (1). An *in vivo* hydrolysable ester of a compound of formula (1) which contains carboxy or hydroxy group is, for example a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid or alcohol. Such esters can be identified by administering, for example, intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluid.

Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically-acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in-vivo* hydrolysable ester forming groups for hydroxy include C_{1-10}alkanoyl, for example acetyl; benzoyl; phenylacetyl; substituted benzoyl and phenylacetyl, C_{1-10}alkoxycarbonyl (to give alkyl carbonate esters), for example ethoxycarbonyl; di-(C_{1-4})alkylcarbamoyl and *N*-(di-(C_{1-4})alkylaminoethyl)-*N*-(C_{1-4})alkylcarbamoyl (to give carbamates); di-(C_{1-4})alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, (C_{1-4})alkylaminomethyl and di-((C_{1-4})alkyl)aminomethyl, and morpholino or piperazino linked

from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting in-vivo hyrolysable esters include, for example, $R^A C(O)O(C_{1-6})$alkyl-CO-, wherein R^A is for example, benzyloxy-(C_{1-4})alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-(C_{1-4})piperazino-(C_{1-4})alkyl, piperazino-(C_{1-4})alkyl and morpholino-(C_{1-4})alkyl.

In this specification the term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *t*-butyl are specific for the branched chain version only. For example, "C_{1-3}alkyl" includes methyl, ethyl, propyl and isopropyl and examples of "C_{1-6}alkyl" include the examples of "C_{1-3}alkyl"and additionally t-butyl, pentyl, 2,3-dimethylpropyl, 3-methylbutyl and hexyl. Examples of "C_{1-8}alkyl" include the examples of "C_{1-6}alkyl" and additionally heptyl, 2,3-dimethylpentyl, 1-propylbutyl and octyl. An analogous convention applies to other terms, for example "C_{2-6}alkenyl" includes vinyl, allyl, 1-propenyl , 2-butenyl, 3-butenyl, 3-methylbut-1-enyl, 1-pentenyl and 4-hexenyl and examples of "C_{2-6}alkynyl" includes ethynyl, 1-propynyl, 3-butynyl, 2-pentynyl and 1-methylpent-2-ynyl.

"C_{3-7}carbocyclyl" is a saturated, partially saturated or unsaturated, monocyclic ring containing 3 to 7 carbon ring atoms wherein a -CH_2- group can optionally be replaced by a -C(O)-. Suitable examples of "carbocyclyl" are cyclopropyl, cyclopentyl, cyclobutyl, cyclohexyl, cyclohexenyl, 4-oxocyclohex-1-yl and 3-oxocyclohept-5-en-1-yl.

The term "halo" refers to fluoro, chloro, bromo and iodo.

Examples of "C_{1-6}alkoxy" include methoxy, ethoxy, propoxy, isopropoxy, butyloxy, pentyloxy, 1-ethylpropoxy and hexyloxy. Examples of "C_{1-6}alkylamino" include methylamino, ethylamino, propylamino, butylamino and 2-methylpropylmino. Examples of "di(C_{1-6}alkyl)amino" include dimethylamino, *N*-methyl-*N*-ethylamino, diethylamino, *N*-propyl-*N*-3-methylbutylamino. Examples of "*N*-(C_{1-6}alkyl)-*N*-(phenyl)amino" include *N*-methyl-*N*-phenylamino, *N*-propyl-*N*-phenylamino and *N*-(2-methylbutyl)-*N*-phenylamino. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" are *N*-methylcarbamoyl, *N*-ethylcarbamoyl and *N*-(2-ethylbutylcarbamoyl. Examples of "*N*-(C_{1-6}alkyl)-*N*-(phenyl)carbamoyl" include *N*-methyl-*N*-phenylcarbamoyl, *N*-butyl-*N*-phenylcarbamoyl and *N*-(3-methylpentyl)-*N*-(phenyl)carbamoyl. Examples of "*N,N*-di(C_{1-6}alkyl)carbamoyl" include *N,N*-dimethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl and *N*-propyl-*N*-(2-methylbutyl)carbamoyl. Examples of "C_{1-6}alkylthio" include methylthio, ethylthio, propylthio, butylthio and 2-methylbutylthio.

"Heteroaryl" is monocyclic or bicyclic aryl ring containing 5 to 10 ring atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen. Examples of heteroaryl include pyrrolyl, furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridaziny, triazinyl, benzfuranyl, benzthieno, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, quinolinyl, isoquinolinyl and naphthiridinyl. More preferably heteroaryl is imidazolinyl, pyrazolyl, thiazolyl and isoxazolinyl.

Examples of "a 3-8 membered ring optionally containing 1, 2 or 3 atoms selected from O, S and NR^8" include azetidinlyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl and tetrahydrodioxanyl.

Examples of "a 4- to 7-membered saturated heterocyclic ring system" include azetidinlyl, pyrrolidinyl, piperidinyl, piperazinyl, homopiperazinyl and morpholinyl.

Where optional substituents are chosen from "1, 2 or 3" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups. An analogous convention applies to substituents chosen from "1 or 2" groups.

Convenient values of R^1, R^2, R^3 and X are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one aspect of the present invention there is provided a compound of formula (1) as depicted above wherein R^1 is C_{1-8}alkyl optionally substituted by 1, 2 or 3 substituents independently selected from phenyl or heteroaryl, wherein phenyl and heteroaryl are optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, $-OR^4$, $-SR^{10}$, C_{1-6}alkyl and trifluoromethyl.

In another aspect of the invention R^1 is benzyl optionally substituted by 1 or 2 substituents independently selected from fluoro, chloro, bromo, methoxy, methyl and trifluoromethyl.

In one aspect of the invention R^2 is C_{1-8}alkyl substituted by 1, 2 or 3 substituents independently selected from hydroxy, amino, C_{1-6}alkoxy, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, *N*-(C_{1-6}alkyl)-*N*–(phenyl)amino, *N*-C_{1-6}alkylcarbamoyl, *N,N*-di(C_{1-6}alkyl)carbamoyl, *N*-(C_{1-6}alkyl)-*N*–(phenyl)carbamoyl, carboxy, phenoxycarbonyl, $-NR^8COR^9$, $-SO_2R^{10}$, $-SO_2NR^5R^6$ and $-NR^8SO_2R^9$.

In another aspect R^2 is C_{1-8}alkyl, such as C_{1-4}alkyl, substituted by 1, 2 or 3 substituents independently selected from hydroxy, amino, C_{1-6}alkoxy, C_{1-6}alkylamino, and di(C_{1-6}alkyl)amino.

In another aspect R^2 is C_{1-4}alkyl substituted by hydroxy.

In a further aspect R^2 is 2-hydroxy-1-methylethyl.

In one aspect of the invention R^3 is hydrogen.

In one aspect of the invention R^4 is hydrogen, C_{1-4}alkyl or phenyl.

In one aspect of the invention R^5 is hydrogen, C_{1-4}alkyl or phenyl.

In one aspect of the invention R^6 is hydrogen, C_{1-4}alkyl or phenyl.

In one aspect of the invention R^{10} is hydrogen, C_{1-4}alkyl or phenyl.

In one aspect of the invention X is hydrogen, halo, cyano, nitro, hydroxy, thio, thiocyano, C_{1-6}alkylthio (optionally substituted by 1 or 2 substituents selected from halo, -OR^{17}, -$NR^{15}R^{16}$), C_{1-8}alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from halo, -OR^4, -NR^5R^6, -$CONR^5R^6$, -$COOR^7$, -NR^8COR^9, -SR^{10}, -SO_2R^{10}, -$SO_2NR^5R^6$ and -$NR^8SO_2R^9$).

In another aspect X is hydrogen.

In another aspect X is $NR^8SO_2R^9$ where R^8 is hydrogen and R^9 is methyl.

In another aspect X is thiocyano.

In a further aspect X is fluoro, chloro, bromo or cyano.

A particular class of compound is of formula (1) wherein;

R^1 is C_{1-8}alkyl optionally substituted by 1, 2 or 3 substituents independently selected from nitrile, phenyl or heteroaryl, wherein phenyl and heteroaryl are optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, -OR^4, -SR^{10}, C_{1-6}alkyl and trifluoromethyl;

R^2 is C_{1-8}alkyl substituted by 1, 2 or 3 substituents independently selected from hydroxy, amino, C_{1-6}alkoxy, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, *N*-(C_{1-6}alkyl)-*N* –(phenyl)amino, *N*-C_{1-6}alkylcarbamoyl, *N,N*-di(C_{1-6}alkyl)carbamoyl, *N*-(C_{1-6}alkyl)-*N* –(phenyl)carbamoyl, carboxy, phenoxycarbonyl, –NR^8COR^9, –SO_2R^{10}, –$SO_2NR^5R^6$ and –$NR^8SO_2R^9$;

R^3 is hydrogen;

R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} R^{15}, R^{16} and R^{17} are independently hydrogen, C_{1-4}alkyl or phenyl; and

X is hydrogen, halo, cyano, nitro, hydroxy, thio, thiocyano, C_{1-6}alkylthio (optionally substituted by 1 or 2 substituents selected from halo, $-OR^{17}$, $-NR^{15}R^{16}$), C_{1-8}alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from halo, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$ and $-NR^8SO_2R^9$);

Or an aryl or heteroaryl; both of which may be optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_{1-6}alkyl or trifluoromethyl.

A preferred class of compound is of formula (1) wherein;

R^1 is benzyl optionally substituted by 1 or 2 substituents independently selected from fluoro, chloro, bromo, methoxy, methyl and trifluoromethyl;

R^2 is C_{1-4}alkyl substituted by hydroxy;

R^3 is hydrogen;

X is fluoro, chloro, bromo or cyano.

Particularly preferred compounds of the invention include:

2-(Benzylthio)-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol

2-(Benzylthio)-5-chloro-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol

2-[(3-Chlorobenzyl)thio]-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol

5-Chloro-2-[(3-chlorobenzyl)thio]-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol

2-[(3-Chlorobenzyl)thio]-4-hydroxy-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-5-pyrimidinyl thiocyanate

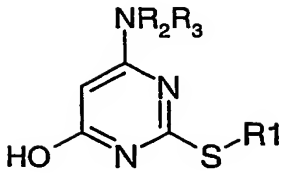
N-(2-[(3-Chlorobenzyl)thio]-4-hydroxy-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-5-pyrimidinyl)methanesulfonamide

2-[(3-Chlorobenzyl)thio]-5-fluoro-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol

2-[(2,3-difluorobenzyl)thio]-4-hydroxy-6{[(1S)-2-hdroxy-1-methylethyl]amino}pyrimidine-5-carbonitrile

and pharmaceutically acceptable salts, solvates or *in vivo* hydrolysable esters thereof. Each of the above mentioned compound and the pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, individually is a preferred aspect of the invention.

The present invention further provides a process for the preparation of a compound of formula (1) as defined above which comprises treating a compound of formula (2):



(2)

wherein R^1, R^2 and R^3 are as defined in formula (1), with suitable electrophiles.

and optionally thereafter (i), (ii), (iii) or (iv) in any order:

i) removing any protecting groups;

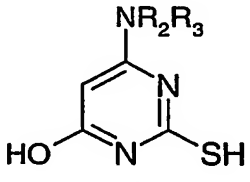
ii) converting the compound of formula (1) into a further compound of formula (1)

iii) forming a salt; and/or

(iv) forming a prodrug.

Reaction of compounds of formula (2) wherein R^1, R^2 and R^3 are as defined in formula (1), with suitable electrophiles include the following representative examples: fluorination (Selectfluor™ in methanol) or chlorination, bromination or iodination (*N*-chlorosuccinimide, *N*-bromosuccinimide or *N*-iodosuccinimide in acetic acid), or bromination (bromine in *N,N*-dimethylformamide) or thiocyanation (by reaction with bromine and potassium thiocyanate) or nitrosation (sodium nitrite in acetic acid) or nitration (nitronium tetrafluoroborate in sulfolane). Further reactions of the nitro or nitroso compounds can then be obtained by reduction to the amine (zinc in acetic acid) and subsequent treatment with either sulfonyl chlorides or acid chlorides to yield alkylsulfonamido- and alkylamido-compounds. Further reactions of the brominated or iodinated compounds with aryl and heteroaryl boronic acids yield compounds of formula (1) where X is aryl or heteroaryl.

Compounds of formula (2) wherein R^1, R^2 and R^3 are as defined in formula (1), can be prepared from compounds of formula (3) wherein R^2 and R^3 are as defined in formula (1) by treatment with alkyl halides R^1A, where R^1 is as defined in formula (1) and A is a halogen, in the presence a suitable base and solvent.

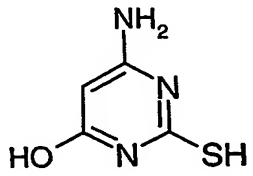


(3)

Examples of suitable bases include the alkali metal hydroxides such as Li, Na, or K. Suitable solvents include *N,N*-dimethylamides, 1-methyl-2-pyrolidone, ethers such as

tetrahydrofuran, 1,4-dioxane, glyme and diglyme and alcohols such as methanol, ethanol and *tert*-butanol. Preferably potassium hydroxide in *N,N*-dimethylformamide at ambient temperature is employed.

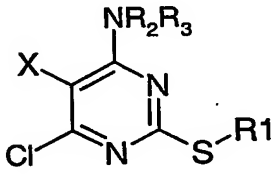
Compounds of formula (3) wherein $R^2$and R^3 are as defined in formula (1);



(4)

may be prepared by reaction of compound (4) with amines HNR^2R^3 where R^2 and R^3 are as defined in formula (1) in the presence of acetic acid at a temperature of 150 – 200°C.

The present invention further provides a process for the preparation of a compound of formula (1) as defined above, where X is CN, which comprises treating a compound of formula (5):



(5)

wherein R^1, R^2 and R^3 are as defined in formula (1), with aqueous base, and optionally thereafter (i), (ii), (iii) or (iv) in any order:

i) removing any protecting groups;

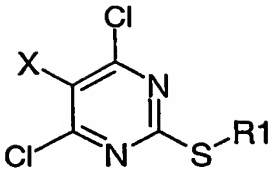
ii) converting the compound of formula (1) into a further compound of formula (1)

iii) forming a salt; and/or

(iv) forming a prodrug.

Examples of suitable bases include sodium methoxide, potassium *tert*-butoxide and the alkali metal hydroxides such as Li, Na, or K. Preferably potassium *tert*-butoxide in aqueous toluene at reflux is employed.

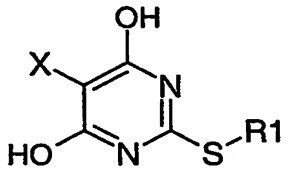
Compounds of formula (5) wherein R^1, R^2 and $R^3$are as defined in formula (1) and X is CN can be prepared from compounds of formula (6) wherein R^1 is as defined in formula (1) by treatment with amines R^2R^3NH in the presence a suitable base and solvent.



(6)

Examples of suitable bases include trialkylamines, such as triethylamine or *N,N*-diisopropylethylamine. Suitable solvents include *N,N*-dimethylamides, 1-methyl-2-pyrolidone, and ethers such as tetrahydrofuran, 1,4-dioxane, glyme and diglyme. The temperature of the reaction can be performed between 0°C and 100°C. Preferably triethylamine in *N,N*-dimethylformamide at room temperature is used.

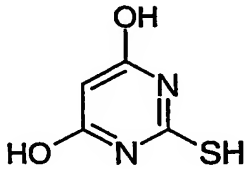
Compounds of formula (6) wherein R^1 is as defined in formula (1) and X is CHO;



(7)

may be prepared by reaction of compounds of formula (7) wherein R^1 is as defined in formula (1) with a halogenating agent such as phosphorous oxychloride followed by reaction with hydroxylamine and then thionyl chloride.

Compounds of formula (7) wherein R^1 is as defined in formula (1);



(8)

may be prepared by reaction of compounds of formula (8) with alkylhalides R_1A where R_1 is as defined in formula (1) and A is halogen in the presence of a suitable base and solvent followed by reaction by Vilsmeir formylation using *N,N*-dimethylformamide and phosphorus oxychloride. Examples of suitable bases include the alkali metal hydroxides such as Li, Na, or K. Suitable solvents include *N,N*-dimethylamides, 1-methyl-2-pyrolidone, ethers such as tetrahydrofuran, 1,4-dioxane, glyme and diglyme and alcohols such as methanol, ethanol and *tert*-butanol. Preferably sodium hydroxide in ethanol at 60°C is employed.

It will be appreciated by those skilled in the art that in the process described above the functional groups of intermediates and starting compounds may need to be protected by protecting groups as described hereinbefore.

Compounds of formulae (4) and (8) are either commercially available, are well known in the literature or may be easily prepared using known techniques.

A compound of formula (1) may be prepared from another compound of formula (1) by chemical modification. Examples of chemical modifications include standard alkylation, arylation, heteroarylation, acylation, sulphonylation, phosphorylation, aromatic halogenation and coupling reactions. These reactions may be used to add new substituents or to modify existing substituents. Alternatively , existing substituents in compounds of formula 1 may be modified by, for example, oxidation, reduction, elimination, hydrolysis or other cleavage reactions to yield other compounds of formula (1).

The compounds of formula (1) above may be converted to a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as discussed above. The salt is preferably a basic addition salt.

The compounds of formula (1) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially CXCR2) activity, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of chemokines. Examples of such conditions/diseases include:

(1) **(the respiratory tract)** obstructive airways diseases including chronic obstructive pulmonary disease (COPD); asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behchet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopical dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(central and peripheral nervous system)** Neurodegenerative diseases and dementia disorders, e.g. Alzheimer's disease, amyotrophic lateral sclerosis and other motor neuron diseases, Creutzfeldt-Jacob's disease and other prion diseases, HIV encephalopathy (AIDS dementia complex), Huntington's disease, frontotemporal dementia, Lewy body dementia and vascular dementia; polyneuropathies, e.g. Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, plexopathies; CNS demyelination, e.g. multiple sclerosis, acute disseminated/haemorrhagic encephalomyelitis, and subacute sclerosing panencephalitis; neuromuscular disorders, e.g. myasthenia gravis and Lambert-Eaton syndrome; spinal diorders, e.g. tropical spastic paraparesis, and stiff-man syndrome: paraneoplastic syndromes, e.g. cerebellar degeneration and encephalomyelitis; CNS trauma; migraine; and stroke.

(6) **(other tissues and systemic disease)** atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, and idiopathic thrombocytopenia pupura; post-operative adhesions, and sepsis.

(7) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(8) Cancers, especially non-small cell lung cancer (NSCLC), malignant melanoma, prostate cancer and squamous sarcoma, and tumour metastasis, non melanoma skin cancer and chemoprevention metastases;

(9) Diseases in which angiogenesis is associated with raised CXCR2 chemokine levels (e.g. NSCLC, diabetic retinopathy);

(10) Cystic fibrosis;

(11) Burn wounds & chronic skin ulcers;

(12) Reproductive Diseases (e.g. Disorders of ovulation, menstruation and implantation, Pre-term labour, Endometriosis);

(13) Re-perfusion injury in the heart, brain, peripheral limbs and other organs, inhibition of atherosclerosis.

Thus, the present invention provides a compound of formula (1), or a pharmaceutically-acceptable salt, solvate or an *in vivo* hydrolysable ester thereof, as hereinbefore defined for use in therapy.

Preferably the compounds of the invention are used to treat diseases in which the chemokine receptor belongs to the CXC chemokine receptor subfamily, more preferably the target chemokine receptor is the CXCR2 receptor.

Particular conditions which can be treated with the compounds of the invention are rheumatoid arthritis, diseases in which angiogenesis is associated with raised CXCR2 chemokine levels, and COPD.

As a further aspect of the present invention, certain compounds of formula (1) may have utility as antagonists of the CX3CR1 receptor. Such compounds are expected to be

particularly useful in the treatment of disorders within the central and peripheral nervous system and other conditions characterized by an activation of microglia and/or infiltration of leukocytes (e.g. stroke/ischemia and head trauma).

In a further aspect, the present invention provides a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined for use as a medicament.

In a still further aspect, the present invention provides the use of a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined for use as a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial.

In a still further aspect, the present invention provides the use of a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined for use as a medicament for the treatment of rheumatoid arthritis, psoriasis and COPD.

In a further aspect, the present invention provides the use of a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In a still further aspect, the present invention provides the use of a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial.

In a still further aspect, the present invention provides the use of a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of rheumatoid arthritis, psorisis and COPD.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating a chemokine mediated disease wherein the chemokine binds to a chemokine (especially CXCR2) receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula , or a

pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester, as hereinbefore defined.

The invention also provides a method of treating an inflammatory disease, especially RA, COPD and psoriasis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated..

The compounds of formula (1) and pharmaceutically acceptable salts, solvates or in vivo hydrolysable esters thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which formula (1) compound/salt/solvate/ester (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

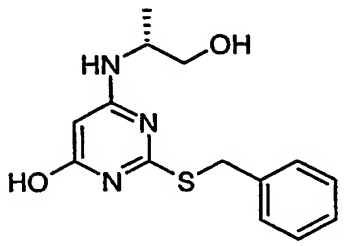
The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compounds of the invention are administered orally.

In addition to their use as therapeutic medicines, the compounds of formula (1) and their pharmaceutically acceptable salts, solvate or *in vivo* hydrolysable esters are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effect of chemokine modulation activity in labatory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

The invention will now be further illustrated by reference to the following non-limiting examples. In the examples the Nuclear Magnetic Resonance (NMR) spectra were measured on a Varian Unity Inova 300 or 400 MHz spectrometer and the Mass Spectrometry (MS) spectra measured on a Finnigan Mat SSQ7000 or Micromass Platform spectrometer. Where necessary, the reactions were performed under an inert atmosphere of either nitrogen or argon. Chromatography was generally performed using Matrex Silica 60® (35-70 micron) or Prolabo Silica gel 60® (35-70 micron) suitable for flash silica gel chromatography. High pressure liquid chromatography (HPLC) purification was performed using either a Waters Micromass LCZ with a Waters 600 pump controller, Waters 2487 detector and Gilson FC024 fraction collector or a Waters Delta Prep 4000 or a Gilson Auto Purification System. The abbreviations m.p. and DMSO used in the examples stand for melting point and dimethyl sulphoxide respectively.

Example 1

2-(Benzylthio)-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol



1M aqueous sodium hydroxide (6ml) followed by benzyl bromide (0.71ml) was added to a solution of the product of Example 1 step i) (1.0g) in ethanol (20ml). The mixture was stirred for 2h, the volatiled removed under reduced pressure and the residue purified by silica gel chromatography (10% methanol/dichloromethane) to yield the title product as a white solid. Yield 0.45g.

MS APCI (+ve) 292 $[M+H]^+$

^1H NMR $\delta_{(DMSO)}$ 7.45 - 7.20 (5H, m), 6.72 (1H, br, d), 5.0 (1H, br, t), 4.76 - 4.67 (2H, br, m), 4.35 (2H, s), 3.46 - 3.24 (2H, m), 1.08 (3H, d).

The intermediates for this compound were prepared as follows:

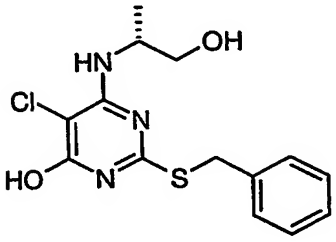
i) 6-{[(1R)-2-hydroxy-1-methylethyl]amino}-2-mercapto-4-pyrimidinol

6-Amino-2-mercapto-4-pyrimidinol (16.1g), acetic acid (14.3ml) and (2R)-2-amino-1-propanol (39ml) were heated at 170°C for 5h. The mixture was cooled to approximately 50°C, diluted with water (500ml) and cooled at 0°C for 20h. The resulting solid was filtered, washed with water and dried *in vacuo* to yield a mixture of product and starting material (2:1) as a cream coloured solid. Yield 7.2g.

MS APCI (+ve) 202 $[M+H]^+$

Example 2

2-(Benzylthio)-5-chloro-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol



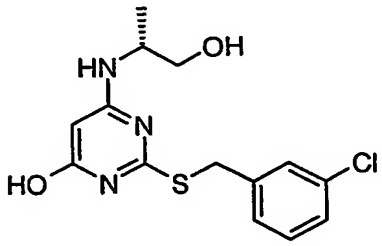
The product of Example 1 (0.5g) was dissolved in acetic acid (10ml), *N*-chlorosuccinamide (0.23g) added and stirred for 3h. The mixture was evaporated and purified by silica gel chromatography (5% methanol/dichloromethane) to yield the title product as a white solid. Yield 0.42g.

MS APCI (+ve) 326 $[M+H]^+$

^1H NMR $\delta_{(DMSO)}$ 12.36 (1H, s), 7.44 - 7.22 (5H, m), 6.29 (1H, d), 4.79 (1H, t), 4.39 (2H, s), 4.25 (1H, m), 3.52 - 3.32 (2H, m), 1.12 (3H, d).

Example 3

2-[(3-Chlorobenzyl)thio]-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol



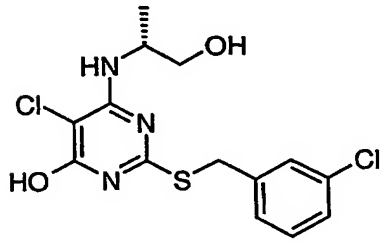
The product of Example 1 step i) (2.0g) was dissolved in ethanol (40ml), 1M aqueous sodium hydroxide (12ml) added followed by 3-chlorobenzyl bromide (1.6ml). The mixture was stirred for 2h, the volatiles removed under reduced pressure and the residue purified by silica gel chromatography (10% methanol/dichloromethane) to yield the title product as a white solid. Yield 1.7g.

MS APCI (+ve) 326 $[M+H]^+$

^1H NMR $\delta_{(DMSO)}$ 11.39 (1H, s), 7.50 (1H, s), 7.42 - 7.28 (3H, m), 6.77 (1H, m), 4.99 (1H, t), 4.34 (2H, s), 3.45 - 3.24 (3H, m), 1.08 (3H, d)

Example 4

5-Chloro-2-[(3-chlorobenzyl)thio]-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol



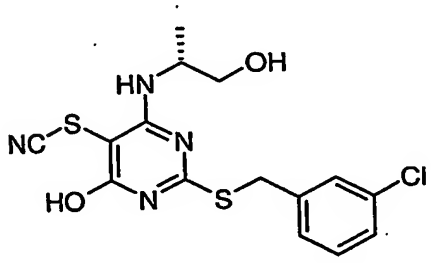
The product of Example 3 (0.22g) was dissolved in acetic acid (10ml), *N*-chlorosuccinamide (0.09g) added and stirred for 3h. The volatiles were removed under reduced pressure and the residue purified by reverse phase HPLC with gradient elution in acetonitrile / 0.02M ammonium hydroxide (90% to 50% aqueous phase) to yield the title product as a white solid. Yield 0.1g.

MS APCI (+ve) 360 $[M+H]^+$

^{1}H NMR $\delta_{(DMSO)}$ 10.33 (1H, s), 7.44 - 7.20 (3H, m), 6.76 (2H, d), 4.78 (1H, m), 4.34 (2H, s), 4.23 (1H, m), 3.51 - 3.23 (2H, m), 1.12 (3H, d).

Example 5

2-[(3-Chlorobenzyl)thio]-4-hydroxy-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-5-pyrimidinyl thiocyanate



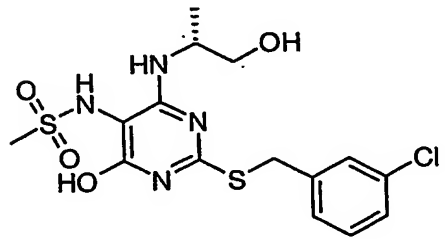
The product of Example 3 (0.5g), pyridine (0.21ml) and potassium thiocyanate (0.6g) were dissolved in *N,N*-dimethylformamide (10ml) and cooled to 0°C. Bromine (0.074ml) was added before the cooling bath was removed and the reaction mixture allowed to warm to room temperature. After 1h water (50ml) was added and the mixture extracted with ethyl acetate (3 x 30ml). The combined extracts were dried over $MgSO_4$, filtered, evaporated and purified by silica gel chromatography (10% methanol/dichloromethane to yield the title product as a white solid. Yield 0.3g.

MS APCI (+ve) 383 $[M+H]^+$

^{1}H NMR $\delta_{(DMSO)}$ 12.54 (1H, s), 7.49 (1H, s), 7.15 (1H, d), 7.42 - 7.31 (3H, m), 4.82 (1H, m), 4.33 (1H, m), 3.53 - 3.36 (2H, m), 1.12 (3H, d), 4.43 (2H, m).

Example 6

N-(2-[(3-Chlorobenzyl)thio]-4-hydroxy-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-5-pyrimidinyl)methanesulfonamide



The product from Example 6 step i) (0.15g) was dissolved in methanol (10ml), 1M aqueous sodium hydroxide (10ml) added and the mixture heated at 80°C for 1h. The mixture was cooled to room temperature, evaporated to approximately 10ml and acidified with 2M hydrochloric acid to yield a white precipitate. The solid was filtered off, washed with water and dried to yield the title product as a white solid. Yield 0.11g.

MS APCI (+ve) 419 $[M+H]^+$

^1H NMR $\delta_{(DMSO)}$ 8.31 (1H, m), 7.43 - 7.27 (3H, m), 7.49 (1H, s), 6.03 (1H, d), 4.80 (1H, m), 4.39 (2H, m), 4.14 (1H, m), 3.48 - 3.25 (2H, m), 2.96 (3H, s), 1.07 (3H, d).

i) 2-[(3-Chlorobenzyl)thio]-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-5-[(methylsulfonyl)amino]-4-pyrimidinyl methanesulfonate

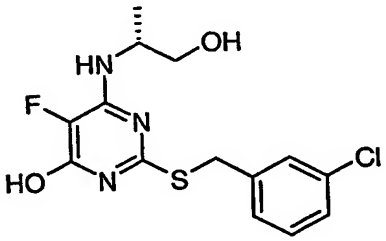
The product of Example 3 (0.9g) was dissolved in acetic acid (12ml) and a solution of sodium nitrite (0.25g) in water (2ml) added dropwise to give a dark blue solution. After 10min the mixture was evaporated, and azeotroped with ethanol (x2). The residue was dissolved in ethanol (50ml), acetic acid (2ml) added and heated to reflux. Zinc dust (2.0g) was added portionwise and the mixture heated at reflux for a further 5min. The mixture was cooled to room temperature, filtered through celite and evaporated. The residue was dissolved in *N,N*-dimethylformamide (10ml), treated with imidazole (0.63g) and *tert*-butyldimethylsilyl chloride (1.35g) and stirred for 24h. The reaction was quenched with water, extracted with ethyl acetate (x 3), dried ($MgSO_4$), filtered and evaporated. The residue was diluted in dichloromethane (50ml) and treated with diisopropylethylamine (4.4ml) and methanesulfonic acid (0.44ml) for 1h before H_2O (10ml) was added. The organics were recovered, dried ($MgSO_4$) and concentrated. The residue was dissolved in tetrahydrofuran (30ml), 1M aqueous sodium hydroxide (5ml) added, stirred for 1h, acidified with 2M hydrochloric acid and stirred for a further 1h. The mixture was adjusted to pH 7 with sodium bicarbonate, extracted with ethyl acetate (x3), dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica gel chromatography (5% methanol/dichloromethane) to yield the product as a white solid. Yield 0.12g.

MS APCI (+ve) 497 $[M+H]^+$

^1H NMR $\delta_{(DMSO)}$ 12.42 (1H, s), 7.50 (1H, s), 6.21 (1H, d), 7.43 - 7.32 (3H, m), 4.42 (2H, m), 4.26 (1H, m), 3.47 (3H, s), 3.44 (3H, s), 3.43 (2H, m), 1.08 (3H, d).

Example 7

2-[(3-Chlorobenzyl)thio]-5-fluoro-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol



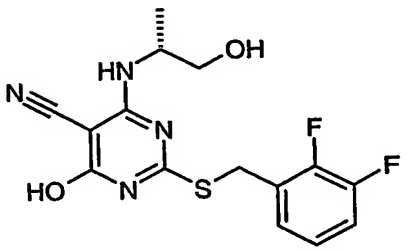
The product of Example 3 (0.1g) was dissolved in methanol (10ml), Selectfluor™ (0.12g) added and stirred for 20h. The mixture was evaporated and purified by silica gel chromatography (5% methanol/dichloromethane) to yield the title product as a white solid. Yield 0.019g.

MS APCI (+ve) 344 $[M+H]^+$

^1H NMR $\delta_{(DMSO)}$ 7.48 (1H, s), 7.40 - 7.29 (3H, m), 6.65 (1H, t), 4.34 (2H, m), 4.13 (1H, m), 3.47 - 3.28 (2H, m), 1.09 (3H, d).

Example 8

2-[(2,3-difluorobenzyl)thio]-4-hydroxy-6{[(1S)-2-hdroxy-1-methylethyl]amino}pyrimidine-5-carbonitrile



To a solution of the product of Example 8 step vi) (0.65g) in toluene (5ml) was added water (24mg) and potassium *tert*-butoxide (0.15g) and the mixture heated at reflux for 3h. The reaction mixture was allowed to stand at room temperature for 16h. The volatiles were removed *in vacuo* and the residue treated with methanol (50ml) and hydrochloric acid (10ml, 1M). The reaction mixture was stirred at room temperature for 3h before the volatiles were

removed *in vacuo* and the residue was neutralised by the addition of saturated sodium bicarbonate. This mixture was extracted with ethyl acetate (2x100ml), the combined organics washed with water (2x20ml), brine (20ml), dried ($MgSO_4$) and concentrated to yield a yellow solid. This material was purified by column chromatography by eluting with ethyl acetate:isohexane (1:1) to ethyl acetate to yield the title compound as a yellow solid (0.170g).

MS APCI (+ve) 394 $[M+CH_3CN]^+$

^1H NMR: (DMSO) δ 12.63 (1H, s), 7.31-7.41 (3H, m), 7.14-7.22 (1H, m), 4.80 (1H, t), 4.41-4.60 (2H, m), 4.10-4.40 (1H, m), 3.35 (2H, m), 1.20 (3H, d).

The intermediates for this compound were prepared as follows:

i) 2-[(2,3-difluorobenzyl)thio]pyrimidine-4,6(1H,5H)-dione

Sodium hydroxide (6.1g) in ethanol (20ml) and water (20ml) was added to a suspension of 4,6-dihydroxy-2-thiopyrimidine in ethanol/water (120ml/120ml). 2,3-difluorobenzyl bromide (28.4g) was added dropwise to this solution. The mixture was heated at 60°C for 2h and stirred at room temperature 20h. The solids were filtered and washed with water (200ml), isopropanol (20ml) and dried *in vacuo* at 40°C for 24h to yield the subtitle compound (31.0g).

MS APCI (+ve) 271 $[M+H]^+$

ii) 4,6-dichloro-2-[(2,3-difluorobenzyl)thio]pyrimidine-5-carbaldehyde

N,N-dimethylformamide (12.9ml) was added dropwise to phosphorus oxychloride (39.6ml) at 5°C. The resulting slurry was stirred at room temperature for 2h. The product of Example 8 step i) was added in portions and stirred at room temperature for 1h. The mixture was then heated at 100°C for 12h. The residue was concentrated *in vacuo* and suspended in water/ice (1:1). The solid formed was extracted with ethyl acetate (2x150ml). The ethyl acetate layers were washed with water (2x100ml), brine(100ml) and dried ($MgSO_4$). The solid was filtered and the filtrate concentrated *in vacuo* to yield a yellow solid. This was purified by column chromatography using ethyl acetate/isohexane (1:9) to yield the subtitle compound (5.0g).

^1H NMR: ($CDCl_3$) δ 10.37 (1H, s), 7.21-7.31 (1H, d), 7.00-7.20 (2H, m), 4.48(2H, S).

iii) 4,6-dichloro-2-[(2,3-difluorobenzyl)thio]pyrimidine-5-carbaldehyde oxime

Hydroxylamine hydrochloride (0.99g) was added to a slurry of the product of Example 8 step ii) (5.0g) in water (1.34ml) and acetic acid (21ml). This mixture was then heated at 60°C for 3h. The reaction mixture was then allowed to come to room temperature and water (20ml) added before cooling to 0°C for 1h and then filtering. The solid obtained was purified by column chromatography eluting with dichloromethane to yield the subtitle compound (1.5g) as a white solid.

MS APCI (+ve) 351 $(M+H)^+$

iv) 4,6-dichloro-2-[(2,3-difluorobenzyl)thio]pyrimidine-5-carbonitrile

The product of Example 8 step iii) (1.5g) in thionyl chloride (50ml) was heated at reflux for 4h. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate (2x50ml) and concentrated under reduced pressure to yield the subtitle compound (1.5g).

^{1}H NMR: ($CDCl_3$) δ 7.20-7.30 (1H, m), 7.26-7.31(1H, s), 7.00-7.20(2H, m), 4.45(2H, S).

v) 4-chloro-2-[2,3-difluorobenzyl)thio]-6-{[(1S)-2-hydroxy-1-methylethyl]-amino}pyrimidine-5-carbonitrile

R-Alaninol (0.96g) in *N,N*-dimethylformamide (5ml) was added dropwise at 0°C to a solution of the product of Example 8 step iv) (1.5g) in *N,N*-dimethylformamide (20ml). The mixture was stirred at room temperature for 30min. and triethyl amine (0.45g) added at 0°C. The mixture was stirred at room temperature for 16h. To the mixture was added water (30ml) and extracted with ethyl acetate (2x100ml). The combined organics were washed with water (2x20ml), brine (20ml) and dried ($MgSO_4$). The solid was filtered and the filtrate concentrared *in vacuo* to give a yellow solid. The solid was purified by column chromatography by eluting with (30% to 50% ethyl acetate/isohexane) to yield the subtitle compound as a yellow solid (1.10g).

MS APCI (+ve) 371 $(M+H)^+$

^{1}H NMR: (DMSO) δ 8.03(1H, d), 7.31-7.4 (2H, m), 7.13-7.20 (1H, m), 4.77 (1H, t), 4.44 (2H, d), 4.28-4.40 (1H, m), 3.35-3.50 (2H, m), 1.15 (3H, d).

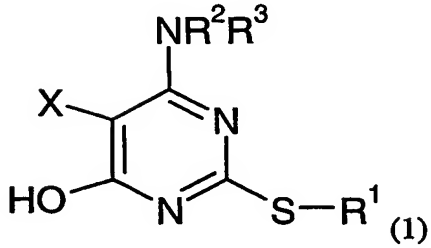
vi) 4-[(1S)-2-{[tert-butyl(dimethyl)silyl]oxy}-1-methylethyl)amino]-6-chloro-2-[(2,3-difluorobenzyl)thio]pyrimidine-5-carbonitrile

Imidazole (0.20g) was added to a solution of the product of Example 8 step v) (1.10g) and *tert*-butyldimethylsilyl chloride (0.45g) in *N,N*-dimethylformamide (10ml) at 0°C. This solution was allowed to warm to room temperature and stirred for 16h. To this mixture were added imidazole (20mg) and *tert*-butyldimethylsilyl chloride (44mg) and the mixture stirred for 2h before water (50ml) was added and extracted with ethyl acetate (2x100ml). The combined organics were washed with water (3x30ml), brine (30ml), dried ($MgSO_4$), filtered and the filtrate evaporated *in vacuo* to yield a yellow solid. This was purified by column chromatography eluting with isohexane and then dichloromethane to yield the subtitle compound as a yellow oil (0.90g).

MS APCI (+ve) 485 $(M+H)^+$

CLAIMS

1. A compound of formula (1), a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof:



(1)

wherein R^1 is a group selected from C_{3-7}carbocyclyl, C_{1-8}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl; wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from fluoro, nitrile, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, phenyl or heteroaryl; wherein phenyl and heteroaryl are optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_{1-6}alkyl and trifluoromethyl;

wherein R^2 is C_{3-7}carbocyclyl, optionally substituted by 1, 2 or 3 substituents independently selected from:

(a) fluoro, $-OR^4$, $-NR^5R^6$ $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$;

(b) a 3-8 membered ring optionally containing 1, 2 or 3 atoms selected from O, S, $-NR^8$ and whereby the ring is optionally substituted by C_{1-3}alkyl or fluoro; or

(c) phenyl or heteroaryl, each of which is optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-NR^8COR^9$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_{1-6}alkyl and trifluoromethyl;

or R^2 is a group selected from C_{1-8}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl wherein the group is substituted by 1, 2 or 3 substituents independently selected from hydroxy, amino, C_{1-6}alkoxy, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, *N*-(C_{1-6}alkyl)-*N* –(phenyl)amino, *N*-C_{1-6}alkylcarbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, *N*-(C_{1-6}alkyl)-*N* –(phenyl)carbamoyl, carboxy, phenoxycarbonyl, $-NR^8COR^9$, $-SO_2R^{10}$, $-SO_2NR^5R^6$ and $-NR^8SO_2R^9$;

wherein R^3 is hydrogen or R^2;

R^4 is hydrogen or a group selected from C_{1-6}alkyl and phenyl, wherein the group is optionally substituted by 1 or 2 substituents independently selected from halo, phenyl, $-OR^{11}$ and $-NR^{12}R^{13}$;

R^5 and R^6 are independently hydrogen or a group selected from C_{1-6}alkyl and phenyl wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, phenyl, $-OR^{14}$,$-NR^{15}R^{16}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-SONR^{15}R^{16}$ and $NR^{15}SO_2R^{16}$

or

R^5 and R^6 together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring system optionally containing a further heteroatom selected from oxygen and nitrogen atoms, which ring system may be optionally substituted by 1, 2 or 3 substituents independently selected from phenyl, $-OR^{14}$, $-COOR^{14}$, $-NR^{15}R^{16}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-SONR^{15}R^{16}$, $NR^{15}SO_2R^{16}$ or C_{1-6}alkyl (optionally substituted by 1 or 2 substituents independently selected from halo, $-NR^{15}R^{16}$ and $-OR^{17}$ groups);

R^{10} is hydrogen or a group selected from C_{1-6}alkyl or phenyl, wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, phenyl, $-OR^{17}$ and $-NR^{15}R^{16}$; and

each of R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14} R^{15}, R^{16}, R^{17} is independently hydrogen, C_{1-6}alkyl or phenyl;

X is hydrogen, halo, cyano, nitro, hydroxy, C_{1-6}alkoxy (optionally substituted by 1 or 2 substituents selected from halo, $-OR^{11}$ and $-NR^{12}R^{13}$), $-NR^5R^6$, $-COOR^7$, $-NR^8COR^9$, thio, thiocyano, C_{1-6}alkylthio (optionally substituted by 1 or 2 substituents selected from halo, $-OR^{17}$, $-NR^{15}R^{16}$), $-SO_2R^{10}$, $-SO_2NR^5R^6$ or a group selected from C_{3-7}carbocyclyl, C_{1-8}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl, wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$ and $-NR^8SO_2R^9$; or an aryl or heteroaryl group, both of which may be optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_1-C_6alkyl or trifluoromethyl groups;

2. A compound according to claim 1 wherein R^1 is C_{1-8}alkyl optionally substituted by 1, 2 or 3 substituents independently selected from nitrile, phenyl or heteroaryl, wherein phenyl and heteroaryl are optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, $-OR^4$, $-SR^{10}$, C_{1-6}alkyl and trifluoromethyl;

wherein R^2 is C_{1-8}alkyl substituted by 1, 2 or 3 substituents independently selected from hydroxy, amino, C_{1-6}alkoxy, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, *N*-(C_{1-6}alkyl)-*N*–(phenyl)amino, *N*-C_{1-6}alkylcarbamoyl, *N,N*-di(C_{1-6}alkyl)carbamoyl, *N*-(C_{1-6}alkyl)-*N*–(phenyl)carbamoyl, carboxy, phenoxycarbonyl, $-NR^8COR^9$, $-SO_2R^{10}$, $-SO_2NR^5R^6$ and $-NR^8SO_2R^9$;

wherein R^3 is hydrogen;

R^4, R^5, R^6, R^8, R^9 and R^{10} are independently hydrogen, C_{1-4}alkyl or phenyl; and

wherein X is hydrogen, halo, cyano, nitro, hydroxy, thio, thiocyano, C_{1-6}alkylthio (optionally substituted by 1 or 2 substituents selected from halo, $-OR^{17}$, $-NR^{15}R^{16}$), C_{1-8}alkyl (optionally substituted by 1, 2 or 3 substituents independently selected from halo, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$ and $-NR^8SO_2R^9$).

3. A compound according to claim 1 wherein R^1 is benzyl optionally substituted by 1 or 2 substituents independently selected from fluoro, chloro, bromo, methoxy, methyl and trifluoromethyl; R^2 is C_{1-4}alkyl, substituted by 1, 2 or 3 substituents independently selected from hydroxy, amino, C_{1-6}alkoxy, C_{1-6}alkylamino, and di(C_{1-6}alkyl)amino; R^3 is hydrogen; X is hydrogen, fluoro, chloro, bromo, thiocyano, $-NR^8SO_2R^9$ (where R^8 is hydrogen and R^9 is methyl) or cyano.

4. A compound selected from the group consisting of:

2-(Benzylthio)-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol

2-(Benzylthio)-5-chloro-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol

2-[(3-Chlorobenzyl)thio]-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol

5-Chloro-2-[(3-chlorobenzyl)thio]-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol

2-[(3-Chlorobenzyl)thio]-4-hydroxy-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-5-pyrimidinyl thiocyanate

N-(2-[(3-Chlorobenzyl)thio]-4-hydroxy-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-5-pyrimidinyl)methanesulfonamide

2-[(3-Chlorobenzyl)thio]-5-fluoro-6-{[(1R)-2-hydroxy-1-methylethyl]amino}-4-pyrimidinol

2-[(2,3-difluorobenzyl)thio]-4-hydroxy-6{[(1S)-2-hdroxy-1-methylethyl]amino}pyrimidine-5-carbonitrile

and a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof.

5. A compound according to any one of claims 1 to 4 for use as a medicament.

6. A compound according to any one of claims 1 to 4 for use as a medicament for the treatment of rheumatoid arthritis.

7. A compound according to any one of claims 1 to 4 for use as a medicament for the treatment of psoriasis .

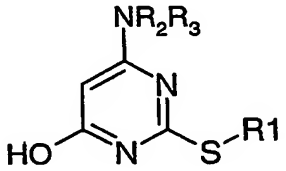
8. A compound according to any one of claims 1 to 4 for use as a medicament for the treatment of COPD.

9. The use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial.

10. The use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for the treatment of rheumatoid arthritis, psoriasis and COPD.

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4; and a pharmaceutically-acceptable diluent or carrier.

12. A process for the preparation of a compound of formula (1) as defined above which comprises treating a compound of formula (2):



(2)

wherein R^1, R^2 and R^3 are as defined in formula (1), with suitable electrophiles.

and optionally thereafter (i), (ii), (iii) or (iv) in any order:

i) removing any protecting groups;

ii) converting the compound of formula (1) into a further compound of formula (1)

iii) forming a salt; and/or

(iv) forming a prodrug.